Assessing Tumor Response in Liver Therapy

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Value of monitoring treatment response

Monitoring tumor response to loco-regional therapy of hepatic tumors is an increasingly important task in oncologic imaging. Early favorable response generally indicates effectiveness of therapy, and may result in significant survival benefit, partially because of achieving local control of the disease. More importantly, withholding treatment once imaging response is achieved will prevent treatment-related toxicities especially in the presence of hepatic cirrhosis in patients with HCC. Since the already diseased cirrhotic liver is exquisitely sensitive to any form of toxic insult, responders may be able to preserve functioning healthy liver tissue for a longer period after therapy, which is also likely to contribute to their prolonged survival. Early identification of treatment failure is also critical in patient management, since a repeat treatment cycle can be performed if liver function is maintained, before disease progression occurs. However, physicians who interpret post-treatment imaging on these patients do not have criteria allowing them to identify tumor necrosis and cell death with absolute certainty because such criteria have been validated. We will discuss the role of CT and MR imaging in evaluating response to the two most commonly available tissue therapies. These are radiofrequency ablation and chemoembolization.

Current standard response criteria and their limitations

I. Response based on change in tumor size.

Change in tumor size on cross-sectional imaging is the gold standard for noninvasive imaging assessment that is utilized to guide clinical decision-making after chemotherapy [1]. These measurements can be performed on CT or MR imaging. Increase in tumor size is consistently associated with disease progression. However, necrotic or fibrotic tumor remnants detected at pathology may not be accurately differentiated from residual tumor by imaging, resulting in underestimation of treatment response. Reduction in tumor size, according to Response Evaluation Criteria in Solid Tumors (RECIST), is a standard and validated means of assessing response to chemotherapy [1, 2]. However, in the early post treatment period decrease in viable cell mass is not necessarily reflected by changes in tumor size, and tumors may not decrease in size following chemoembolization or radiofrequency ablation despite the fact that

they are not viable [3, 4]. In fact, after radiofrequency ablation the size of the treated lesion is usually larger than the size of the lesion prior to treatment, and this indicates complete ablation of the tumor margin, including a safety margin [5, 6]. On subsequent follow up the lesion may remain stable in size, or slowly decrease leaving a small scar. After chemoembolization, there is proven discrepancy between the reduction in tumor size seen on imaging and the degree of necrosis at histopathology [3, 4]. This may be explained by the delayed resorption of the necrotic material due to the occlusion of the feeding artery and hepatic sinusoids. Studies have shown that it may take several weeks to determine the success or failure of a specific chemotherapeutic regimen in a patient if the response to treatment is based on change in tumor size. Therefore, some patients may have ineffective drug administration needlessly until clear progression is observed on cross sectional imaging, or until their clinical symptoms deteriorate.

II. Response based on iodized oil (lipiodol) deposition on CT.

Unenhanced CT is useful for confirming successful introduction of the high-density lipiodol, which is an essential ingredient of the chemoembolization mixture, into the targeted lesions. Intense and prolonged accumulation of lipiodol within tumors has been reported to correlate well with complete tumor necrosis and survival [7-11]. In contrast, poor retention of lipiodol has been shown to indicate persistent tumor viability [7, 8]. In an attempt to estimate tumor necrosis on contrast-enhanced CT, a prior study suggested that tumor necrosis after TACE can be estimated by adding the nonenhancing areas on CT to the areas of lipiodol retention [4]. However, lipiodol distribution is a marker of the presence of chemoembolization mixture and does not quantify the degree of tumor necrosis, which is the main objective of post treatment imaging. We have identified areas of residual enhancement on MR imaging in spite of excellent lipiodol deposition. We have also found that lipiodol distribution often occurs in surrounding liver parenchyma without specifically accumulating in the tumor; yet these tumors may demonstrate complete lack of enhancement on MR imaging. In fact, in a previous study we demonstrated poor correlation between lipiodol deposition and tumor enhancement ($p=0.15$). In our experience the presence of high-density lipiodol impairs the ability to assess for contrast enhancement on CT. Thus, the main value of CT is to document the technical success of the procedure but not to quantify tumor necrosis.

III. Limitations of unenhanced MRI and Positron Emission Tomography (PET).

Iodized oil does not cause signal intensity changes on unenhanced MR imaging [12], and is therefore difficult to detect. Signal changes on conventional (T1 and T2) MR imaging are also non-specific and do not correlate with tumor necrosis. Positron emission tomography (PET) has been used to detect HCC, with overall sensitivity of 50% [13, 14]. However, PET is not used to determine tumor response after therapy due to the high false positive rate. Further, the spatial resolution of PET is low compared to CT/MR imaging resulting in partial volume effects at tumor borders.

Potential role of cellular and molecular imaging in assessing treatment response

Inadequate assessment of early treatment response after loco-regional therapy underscores the need for research dedicated to the utilization of molecular and cellular imaging that could potentially be more sensitive than morphologic tumor evaluation especially in the early post treatment period. The validity of tumor measurements has recently been questioned in view of the emergence of new anticancer therapies, geared at tumor dormancy rather than tumor disappearance. Molecular and cellular imaging markers that could be used to assess treatment response include tissue perfusion, water diffusion and biochemical tissue composition. Changes in these markers occur in vivo within hours/days of exposure to antineoplastic agents, and could potentially be utilized to assess early tumor response.

A. Role of perfusion CT or MR imaging

Assessment of tumor necrosis after chemoembolization or radiofrequency ablation may be performed using contrast-enhanced CT or MR imaging. Enhancement is a reflection of cellular viability [15-17]; areas of tumor enhancement are considered viable, whereas non-enhancing regions reflect tissue necrosis. To address the issue of tumor response after loco-regional therapy, the European Association for the Study of Liver Disease (EASL) has sanctioned the use of lesion enhancement, rather than change is size, as the standard method to determine treatment response [18]. EASL also stated that tumor size measurements might not be accurate since it would not take into account the true extent of tumor necrosis after successful therapy. However, uniform rim enhancement may also result from post-treatment reactive granulation tissue, as has been reported after cryoablation of liver tumors in the animal model [19]. TACE does not typically cause such an intense reaction at the tumor periphery, but enhancing granulation tissue is confounding factor. Hence, a marker that would assess cellularity, such as diffusion MR imaging, may offer additional benefit to accurately assess tumor necrosis.

B. Role of diffusion MR imaging

Diffusion MR imaging and apparent diffusion coefficient (ADC) maps have the ability to provide unique insight about the molecular water composition within a tumor, and may also indicate the degree of tumor viability at the cellular level. Factors that can affect tissue ADC include water content and distribution, cellular density and cell membrane status. Our results and those of other groups demonstrate that diffusion MR imaging is superior to standard T1 and T2 weighted MR imaging [20], and it differentiates benign from malignant lesions [21-23]. The use of diffusion MR imaging to probe tumor response is persuasive, because water diffusion can be used to characterize highly cellular regions from acellular or necrotic regions of tumors. Viable tumors are highly cellular and these cells have intact cell membrane, thus restricting the motion of water molecules and resulting in a decrease in the ADC value. On the other hand, cellular necrosis causes increased membranous permeability allowing free diffusion of water molecules and a marked increase in the ADC value. This technique is able to detect early cellular necrosis prior to regression in tumor size [24, 25]. Recently, diffusion MR imaging has been used to assess tumor response after chemotherapy and radiation therapy [26], and has been used as a

surrogate marker in assessing tumor response to therapy before changes in tumor size occur. Furthermore, ADC values add a quantifiable measure of tumor cell death by directly reporting on the state of water diffusion within the tumor, which is especially valuable because of the wide spectrum of histopathologic findings after TACE, ranging from total viability to complete necrosis [27-29]. Based on these studies and our preliminary results we hypothesized that both perfusion and diffusion MR imaging could determine the extent of tumor cell kill after loco-regional therapy, before changes in tumor size occur. While diffusion MR imaging appears to be a powerful technique that may probe cellular integrity, other molecular markers that could monitor tumor response include MR spectroscopy.

C. Role of MR spectroscopy

In vivo MR spectroscopy is a non-invasive technique that has been successfully utilized in evaluating brain diseases, especially brain tumors [30, 31], and to characterize lesions in the breast [32], kidney [33] and prostate [34]. In addition, MR spectroscopy has been used to evaluate diffuse hepatic disease, such as hepatic steatosis [35], chronic hepatitis [36], and cirrhosis [37], as well as the evaluation of focal liver masses such as hepatic adenoma [38] and effects of chemoembolization treatment [39]. MR spectroscopy can define tissue metabolism and metabolic abnormalities in tumors and the surrounding tissues. Therefore, this novel technique can aid in tissue characterization using metabolic markers of malignancy, and it can depict substantial differences between in vivo spectra of tumor, necrosis and healthy tissue. The most common metabolites that are evaluated are N-acetyl aspartate (NAA) (in brain), choline (Cho), creatine (Cr), and lactate (Lac) concentrations. Hepatic tumors, including HCC, like most tumor types, have high choline content, likely due to increased cell turnover and/or increased cellular density. A prior study suggested that following chemoembolization of HCC, tumors have decrease in choline peak of the spectrum, suggesting cellular necrosis [39]. Decreases in choline have also been observed upon successful treatment of brain tumors, and to increase upon recurrence [40]. Based on these studies we predict that MR spectroscopy can contribute biochemical and molecular parameters to conventional (T1 and T2) liver MR imaging.

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